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Blood Sugar in Diabetes Mellitus*

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The blood sugar is an excellent and useful criterion of the behavior of carbohydrate metabolism. Regulated by normal physiological processes, the sugar of the blood has a constancy within definite limits, and in its behavior like other biological constants it tends to return to its original level when the factor for its alteration is corrected. After the complex carbohydrates are simplified by the digestive enzymes in the gastro-intestinal tract, they are carried as glucose by the portal vein to the liver where a molecular rearrangement takes place and glycogen is formed. This biochemical process is not always in one direction. It is reversible, and it is inferred that the liver can also supply the blood with glucose from the glycogen it has stored. It is obvious, therefore, that the liver plays a most significant role in the metabolism of carbohydrates. It is the carbohydrate storehouse, storing the sugars in the form of glycogen and making excellent use of its savings when the organism is in want of sugars and cannot for various reasons

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obtain them exogenously. Thus, during a meal rich in carbohydrates, the blood sugar will rise, but a considerable proportion of the excess will be withdrawn by the liver, converted to glycogen and stored, only to be reconverted into glucose and thrown into the blood stream if the blood sugar should fall below the physiological level. By this means the blood sugar in health is kept within definite limits. These are 80 to 100 mgm. per cent during a fasting state. After an average meal the blood sugar may rise to 140 mg. per cent while after a concentrated carbohydrate meal the value may rise as high as 170 or 180 mg. per cent. It must be pointed out, that the role of the liver in this regulating process is more or less a passive one, as there are many factors which affect its activity directly or indirectly. Of such factors intimately concerned with carbohydrate metabolism, insulin plays a most dominant role and all of us are well familiar with the clinical picture which results from the lack of production or faulty utilization of this hormone. This profound alteration in the carbohydrate metabolism primarily, is known as diabetes mellitus and in addition to its clinical symptomatology of hunger, loss of weight, thirst, frequency of urination, weakness, transient blurring of vision and distressing pruritus chiefly in women, there is a hyperglycemia and a glycosuria. The liver is no longer capable of maintaining the blood sugar at the physiological level because one of the governing mechanisms, insulin, is insufficient. There is faulty storage of glycogen and faulty oxidation of glucose. The blood sugar begins to rise and when it reaches a level of 170 or 180 mg. per cent sugar will appear in the urine. This is true in the majority of the cases, though I have seen some blood sugars between 200 and 300 mg. per cent without a glycosuria. The rise of the blood sugar does not cease at the levels mentioned, but it may rise to a figure of 1000 mg. and over.

With this brief resumé of normal and abnormal carbohydrate physiology and with the knowledge that insulin can alter some of the abnormalities discussed, we can now proceed to the discussion of the blood sugar in diabetes

mellitus. Some phases of the subject are controversial and some are quite factual. *The most accepted fact is that the blood sugar in diabetes mellitus is elevated and maintained at a highly abnormal level unless treated.* All agree that the sugar in the blood is glucose—and that it is fermentable. Most physiologists do not accept the γ-glucose hypothesis of Winter and Smith. While there is no unanimity of opinion regarding the glycolytic power of diabetic blood as compared with the normal, the preponderance of evidence is that no difference exists.

About ten years ago I interested myself in the subject of glycolysis sharing the view that insulin acted by increasing the glycolytic rate. This was not the case, however, as I proved to my satisfaction that the sugar content of diabetic and normal blood kept at room or incubator temperature disappeared at the same rate. Glycolysis did *not* proceed at a less rapid rate in diabetic bloods. There is no difference of opinion concerning the effect of infections on the blood sugar in diabetes mellitus. All agree that during infections, it is always elevated. All agree that a normal blood sugar is highly desirable in the treatment of diabetes but not many appreciate the fact that under certain conditions a hyperglycemia per se is not deleterious, but may even be desirable. In other words a high blood sugar *without a glycosuria* can be tolerated by patients without any damaging results.

Specifically, the discussion of the blood sugar in diabetes mellitus may be approached from three practical considerations, namely the value of blood sugar analyses from the point of *diagnosis, prognosis,* and *treatment.* From a study of a large group of glycosurias and a correlation of the blood sugar findings with them I am firmly convinced that from a *diagnostic* consideration, blood sugar studies are of the greatest and most valuable aid. The benign glycosurias are too well known to all of us and in such cases a definite diagnosis can only be made by means of blood analyses. It is the usual procedure in cases of glycosuria to examine the blood for its glucose content in a post-absorptive state and if the result of such an analysis prove inconclusive then

the patient is subjected to any of the well known tolerance tests. The one most widely in use is the so-called glucose tolerance test. The patient is given 50 to 100 gms. of glucose and the blood is examined for its sugar concentration at a fasting, ½, 1, 2 and 3 hour interval. In the normal individual the maximum rise may reach 180 mg. per 100 c.c. At the end of an hour the concentration of blood glucose begins to fall so that at the end of the third hour there may be less glucose in the blood stream than at its beginning of the test. In the diabetic, on the other hand, the fasting blood sugar is usually above the normal level and even if it is reduced to a normal figure by means of diet, insulin or both, a glucose tolerance test, may send the blood sugar up to 300 and 400 mg. even at the end of the third hour.

There are certain cases where the blood sugar may reach a level of 200 at the end of the first hour and a glycosuria may appear at this point, but the curve falls sharply and conforms to the configuration accepted as normal. I do not consider such curves pathognomonic of diabetes. Now all of this is quite familiar, and yet there is an important consideration which must be weighed in the evaluation of any carbohydrate tolerance test, namely the patient's previous diet.

Some years ago a group of Scandinavian[1] observers called attention to the fact that even in normal individuals a 24 hour fast, or a high-fat-low carbohydrate diet will so alter the character of a tolerance blood sugar curve that a false diagnosis of diabetes will be made. I[2] have had the opportunity of performing such an experiment on two men whose diet consisted of protein and fat—an exclusive meat diet. In both subjects typical diabetic curves were produced following the ingestion of 100 grams of glucose. In one of the men there was a glycosuria as well. The use of a general diet for a two week period cured this artificial diabetes as the repetition of the glucose tolerance test at the end of that time failed to reveal any abnormality. It is obvious therefore that the blood sugar is of considerable diagnostic aid in cases of glycosuria, either as a single fasting specimen

or as a series of specimens after a tolerance test. In the vast majority of cases it will help establish, or rule out the diagnosis of diabetes mellitus. I also wish to lay particular emphasis on the consideration of the patient's diet prior to the performance of a tolerance test since it plays such a significant role in the proper evaluation of the resulting blood sugar curve. Diseases of the liver may also be responsible for abnormal glucose tolerance curves and before accepting a curve as significant of diabetes one must make certain that no liver pathology is present.[13]

Is the blood sugar of any prognostic significance? Does the routine estimation of the blood sugar in diabetes mellitus help in the evaluation of the severity of a case? I do not think it does. Some ten years ago Petren[3] attempted to use the blood sugar as a measure of severity and he considered an initial value of 240 mg. or over as an indication of a severe diabetes. Gray[4] pursuing this trend of thought attempted to show the relation of the percentage of the blood sugar when the patient was first seen, to the duration of such a patient's life. From his studies Gray concluded that the higher the blood sugar, the more severe the diabetes. This point of view has been rather universally accepted, but it certainly can stand revision. It requires time and observation of any given case of diabetes before a prognosis can be given intelligently. It certainly is most fallacious to prognosticate from a blood sugar examination alone. I do not consider an initial blood sugar of 300 mg. of more ominous prognostic significance than one of 200 or 150. The deduction that I draw from such figures in the absence of any infection is that the higher blood sugar may be a reflection of the patient's carelessness in executing dietary directions. Joslin,[5] from whose clinic Gray published the data referred to, now feels that the prognosis in a diabetic case can not be determined by the result of the blood sugar test. He cites a diabetic patient who on admission showed a blood sugar of 400 mg. and a glycosuria of 4.8 per cent whose health 20 months later was excellent and whose diet consisted of protein 75, fat 100, carbohydrate 250 and only 6 units of insulin. "One can not tell

from an initial blood sugar," says Joslin, "the outcome of a case though this was not the rule before the discovery of insulin." This fact was fully appreciated by Petren and his coworkers, and, because of this inadequacy of a single blood sugar determination as a prognostic guide, they have attempted to evaluate the severity of the diabetes from a study of the 24 hour blood sugar curve. Blood samples were taken at two hourly intervals during a 24 hour period and the character of the curve served as an index of severity. They have worked out such blood sugar curves for fast days and food days. They also demonstrated that the blood sugar in certain cases of diabetes is subject to tremendous oscillations during a 24 hour period. All these data are of considerable interest, but I question their applicability, as it is not practical to carry out 24 hour blood sugar analyses in most cases, even though this procedure might afford a trustworthy indication of severity. It is my feeling that response to therapy is a much more reliable index of severity, and no single blood sugar determination regardless of its magnitude will dampen my optimism if the patient's glycosuria diminishes, if he gains in weight and strength and if he is able to tolerate more carbohydrates and total calories without any, or additional units insulin.

Now as to the value of blood sugar studies in the *treatment* of diabetes mellitus. I am in accord with the school of diabetologists who advocate a normoglycemia. A normal blood sugar in a diabetic is usually accompanied by a sugar free urine. That is the optimum goal. Given, however, a sugar free urine, but with a blood sugar level of 200 or 250, is it advisable in such cases to aim at lowering these blood sugars even though no sugar is excreted? I do not think so. There is no clear evidence that a hyperglycemia without a glycosuria is damaging, and, furthermore, such a condition may even be desirable in a certain group of diabetic patients. This view may sound unorthodox but a review of the available evidence will help dissipate doubts concerning this assertion.

In the August number of the Journal of the American Medical Association, Mosenthal[6] in a publication entitled "Hyperglycemia," presents evidence bearing upon this question. Therein, he cites the works of Kirby, Estey and Weiner and that of Carrel showing that culture media containing three to four times the normal concentration of glucose do not inhibit or interfere with growth of tissues. He also presents the work of other investigators who claim that bacteria do not grow more rapidly in culture media of high sugar concentrations. Furthermore, he cites the fact that addition of dextrose to blood does not alter its bactericidal potency against staphylococci, nor make growth of this organism more luxurious.

The above data certainly offer striking evidence that under certain experimental states a hyperglycemia in vitro is not deleterious. Then there are other experimental conditions demonstrating the benefits of a hyperglycemia. Bayliss, Müller and Starling[7] showed that in order to maintain heart-lung preparations in good condition insulin and glucose had to be used and that in the absence of insulin, *enormous concentrations of glucose were required* to compensate for the insulin lack. Cruikshank and Shrivastava[8] showed that the sugar utilization of the heart is increased, by insulin, or *by maintaining a high blood sugar concentration.* In other words a hyperglycemia may act as a compensatory mechanism. Clinical observation has given ample support to these experiments. During the past 4 or 5 years observers from various parts of the country have noted that in some cases of diabetes mellitus lowering of the blood sugar, not necessarily to hypoglycemic levels, was associated with symptoms referable to the heart. Levine[9] of Boston issues unequivocal warning against the rapid reduction of a hyperglycemia in a diabetic with coronary artery disease. I have seen one death associated with the use of insulin in a diabetic, who was also suffering from coronary sclerosis. Even though there was a temporal relationship I was not convinced that it was cause and effect as cases of coronary sclerosis may also die without any apparent cause. However, the work of Strouse[10] and his associates on this

subject, made me feel that some such relationship exists. They found that in the older diabetic a marked reduction of the blood sugar whether by insulin or diet was associated with manifestations of cardiac abnormalities such as paroxysmal auricular fibrillation, intraventricular block and the clinical picture of angina. Sherrill[11] of California advises that the hyperglycemia of the elderly diabetic, particularly when evidences of atherosclerotic changes are demonstrable, be handled most conservatively. We thus see from the data presented that hyperglycemia does not interfere with or inhibit tissue growth, that hyperglycemia does not furnish some bacteria—staphylococci—a more fertile soil for growth, and that hyperglycemia may be of benefit in the elderly diabetic patient, who reveals evidence of vascular disease. I have seen a considerable group of diabetics in their fifth and sixth decades whose blood sugars were twice the normal, but whose urines were free from sugar. These patients maintained their weight, they were symptom free and carried on with their daily routine. But as soon as continuous glycosuria set in because of dietary indiscretions or infections then, and only then did symptoms of diabetes become apparent. In certain cases of diabetes mellitus a hyperglycemia without a glycosuria is seen and in such cases it is my feeling that a *sugar free urine is a satisfactory criterion of good therapy* from the laboratory view point. With younger diabetics under such circumstances the blood sugar will in the majority of cases approach the normal figure; in the older diabetic let the blood sugar seek its own level, even though it is above the figure considered normal.

This point of view will no doubt bring forth the criticisms that good therapy must not only ameliorate suffering, it must also prevent complications and a high blood sugar even without a glycosuria may lead to undesirable sequelae, which according to popular medical opinion of many years, are—infections as immediate complications and atherosclerosis as remote. I am not referring to the diabetic who is spilling sugar, I have in mind the patient who has only the hyperglycemia. Is this type of patient more subject to

infections and atherosclerosis than the diabetic with a normoglycemia? From my observations and experience he is not. True I have seen nail infection, boils, tuberculosis, pneumonia, otitis media, mastoiditis and common colds in our group of diabetics, but I do not think that such infections were more prevalent among these patients, than any group of individuals under similar living conditions, and many of our patients revealed hyperglycemic states—some with and some without glycosurias. It is my feeling that this association of infections and diabetes has become so deeply rooted, with the resulting view point that hyperglycemia renders the patient more susceptible to infectious processes. Mosenthal is of the opinion that the tissue dessication and the debility resulting from a persistent glycosuria predipose the patient to infections and that the hyperglycemia per se is not deleterious. Infections, however, no matter how slight, affect adversely the carbohydrate tolerance and are therefore dreaded as complications. Now as to the complication of atherosclerosis. Does a high blood sugar alone favor or hasten the development of vascular sclerosis? No one really knows. The hypotheses are multiple, conflicting and confusing. The experimental evidence of MacLeod[12] failed to corroborate this postulate. He maintained two depancreatized dogs in a state of hyperglycemia and glycosuria for 4 years and was unable to demonstrate any arterial sclerosis. The more fashionable thought is to associate a hypercholesterolemia and ketonemia with atherosclerosis, and furthermore there are many who feel that in an individual with vascular sclerosis and diabetes, the diabetes may be the result and not the cause. With such conflicting concepts regarding the damaging affects of a hyperglycemia and with so much evidence that it may be of benefit in a certain group of diabetic patients is it essential in the treatment to insist on normal blood sugar value, having rendered the urine free from sugar? The patient is the one who can best guide us in this respect. If he feels well, is able to carry on, maintains his weight and is satisfied with the dietary prescription and at the same time does not excrete sugar I do not advocate any

further dietary change or the use of insulin to reduce the blood sugar, should it be found above the accepted normal value. The argument has been advanced that it is wise to reduce the blood sugar to its normal level, regardless of the urinary findings, because it represents a physiological state. In the non-diabetic such a hypothesis is tenable. In the diabetic I feel that a moderate hyperglycemia may represent the organism's adaptation to an abnormal situation. No one will deny that a heart of normal size is most desirable but that under certain conditions its hypertrophy serves a useful purpose. This is just one of many examples of bodily adaptations to pathological states and I feel that a mild hyperglycemia is another, and should not be too zealously treated as long as the urine is free from sugar.

To summarize I conclude as follows:

1. The determination of the blood sugar is of greatest value in the *diagnosis* of diabetes mellitus. This determination is of help as a single fasting specimen or as a series of specimens following any of the tolerance tests. In the evaluation of such tests diseases of the biliary tract and the previous diets of the patient must be reckoned with.

2. A single blood sugar determination is of little value in determining the severity or prognosis of a case of diabetes mellitus.

3. In the treatment a sugar free urine is a satisfactory laboratory criterion. In the young diabetic the blood sugar will approximate normality under such conditions; in the older patient let the blood sugar seek its level, even though high. There is little evidence to prove that such a hyperglycemic state is deleterious and there is considerable evidence that it is desirable.

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Discussion

Dr. Elaine Ralli: Mr. Chairman, fellow members: I am very glad to have been asked to discuss these papers this evening and I must say it is very easy because I am in entire agreement with practically everything that the three speakers have said. I should like to stress one or two points. If I may go back to one of the points that Dr. Himwich brought out in his paper, that is the matter of dehydration. It is a peculiar thing that although dehydration has been spoken of repeatedly, Dr. Himwich showed it very beautifully here in 1933 at the Graduate Fortnight, Atchley has reported it, and Peters and his collaborators have written on the subject, that too little attention has been paid to it clinically as probably one of the most important factors in diabetic ketosis. The importance of dehydration is borne out by the fact that treatment of diabetic coma by insulin alone, although it may clear up the ketosis, will not always return the patient to a conscious state, and the additional injection of saline intravenously will bring back consciousness, which from the patient's point of view, is a very desirable state to be in. We recently had an opportunity of observing a case in which the dehydration and anhydremia were unusually severe because of a preceding period of starvation which antedated even the ketosis. The CO_2 combining power was 17.06 per cent and the blood sugar high. Here again I agree with Doctors